

Symptom Triad May Identify Parkinson's Risk

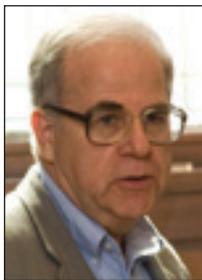
BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES

BARCELONA – Severe hyposmia may be associated with a deficiency of striatal dopamine transporter protein and slight cognitive decline – characteristics that could identify people with an increased risk of developing Parkinson's disease, according to preliminary findings from the Parkinson's Associated Risk Study.

"This is an interesting observation: [Cognitive] decline may be occurring well in advance of motor symptoms," Dr. Kenneth Marek said at the conference. "This might be something we could use to predict who will develop dopamine transporter deficiency and, eventually, symptomatic Parkinson's."

The prospective PARS (Parkinson's Associated Risk Study) aims to test the effectiveness of two biomarkers – sense of smell and dopamine transporter imaging – in identifying subjects who are at risk of developing the disease. First-degree relatives of Parkinson's disease patients and control subjects will be followed for 2 years to determine whether a deficiency in striatal dopamine transporter (DAT) increases their disease risk.



Dr. Marek and his coinvestigators recruited subjects by a mass mailing of the UPSIT (University of Pennsylvania Smell Identification Test); those scoring in the 15th percentile and lower are invited to participate. So far, 9,400 tests have been mailed out, half to relatives of patients and half to subjects recruited by community notices. About 5,000 have sent the test back.

"We have identified 650 people who were hyposmic below this 15th percentile," said Dr. Marek, president and senior scientist at the Institute for Neurodegenerative Disorders in New Haven, Conn. "This is considered rather severe hyposmia and, interestingly, only about a third of these folks noticed that they even had this symptom."

He presented data on 303 participants (203 hyposmic, 100 normosmic) who had undergone the baseline evaluation. Tests included a neuropsychological test battery, early Parkinson's symptom score, and SPECT (single-photon emission CT) brain imaging of striatal DAT binding with the imaging compound iodine-123-beta-CIT. The study is grouping participants according to their striatal DAT levels: Greater than 80% is considered normal, 65%-80% is considered indeterminate, and less than 65% is considered a deficiency consistent with Parkinson's disease.

Of the 203 hyposmic subjects, 11% had a DAT level less than 65%, compared with 1% of the normosmic group, a significant

VITALS

Major Finding: Significantly more individuals with hyposmia had DAT levels of 65% or lower, compared with normosmic individuals (11% vs. 1%).

Data Source: Preliminary findings among 303 participants in PARS.

Disclosures: The study is sponsored by the U.S. Department of Defense, the Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation. As an employee of the Institute for Neurodegenerative Disorders, Dr. Marek participates in multiple clinical studies, some of which are funded by drug companies.

difference. "That one person in the normosmic group also has a REM sleep behavior disorder," Dr. Marek noted.

Indeterminate DAT levels were seen in 17% of the hyposmic and in 7% of the normosmic groups, and normal levels were seen in 71% of the hyposmic and 92% of the normosmic groups. (Percentages in the

Hyposmia, loss of dopamine transporters, and cognitive decline might predict risk for symptomatic Parkinson's.

DR. MAREK

hyposmic group do not equal 100% because of rounding.)

Bowel habits also varied significantly between the groups. Nearly half (48%) of those with the lowest DAT density reported fewer than one bowel movement

per day, compared with 21% of the normal-level group. Conversely, 13% of the lowest-level group reported one or more bowel movements per day, compared with 51% of the normal-level group.

"Similarly, [the lowest DAT-level group was] much more likely to endorse questions related to REM sleep behavior disorder," Dr. Marek said. "And when we used another tool – a nine-item symptom rating scale that assesses early Parkinson's – those individuals in the lowest DAT group were more likely to endorse the symptoms."

Taking these data into account, he said it seems as if "these individuals express a number of features that we might call 'premotor Parkinsonism.'"

The researchers have completed cognitive testing on 131 participants (17 with decreased DAT levels and 114 with normal levels). Mean age was the same (68 years) in both groups and their educational levels were not significantly different.

"Even in this group, [in which all the] subjects were entirely cognitively normal, it was possible to distinguish individuals based on their cognitive function related to whether they had this early DAT deficit or not," Dr. Marek said. "I would not call them cognitively impaired, because they were not, but they were different and easily distinguished, based on their scores and imaging outcomes." ■

Manganese Exposure May Boost Risk for Parkinsonism

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES

BARCELONA – Long-term welding work may be a risk factor for developing parkinsonism – perhaps because manganese can travel directly into the midbrain via the olfactory nerve.

Two recent studies suggest a dose-response association, with increased risk as years of exposure accumulate.

"Manganese, in particular, has been shown to be a neurotoxin," said Jessica Lundin, a PhD candidate at the University of Washington, Seattle, who presented early findings from a cross-sectional study during a poster session at the meeting. "There is some evidence that it enters via an olfactory route."

The metal is a large component of fumes created by the welding process. According to the Centers for Disease Control and Prevention, "Prolonged exposure to high manganese concentrations (greater than 1 mg/m³) in air may lead to a Parkinsonian syndrome known as manganism. Chronic exposure to the manganese-containing pesticides is also reported to cause Parkinson-like symptoms."

Recent studies have also indicated that long-term exposure to inhaled manganese is associated with neurologic and neurobehavioral deficits, according to the agency. "These effects include changes in mood and short-term memory, altered reaction time, and reduced hand-eye coordination. Affected workers frequently show abnormal accumulations of manganese in a region of the brain known as the globus pallidus."

Ms. Lundin and her colleagues recruited 581 welders from three U.S. shipbuilding sites for a 3-year follow-up study. All welders underwent a baseline neurologic assessment by a movement disorders specialist. Assessments in the National Institute of Environmental Health Sciences-sponsored study included the Unified Parkinson's Disease Rating Scale (motor subsection 3), timed motor tasks, and a questionnaire about occupational history (including prior welding jobs), lifestyle, and medical history, including smoking and neurotoxic exposure, especially to pesticides.

At baseline, individuals in the cohort had a mean age of 45 years and had welded for a mean of 23,000 hours. Individuals in the study were considered to be normal if their UPDRS3 scores were 6 or less; to be mildly affected by parkinsonian symptoms with scores of

6-14; and to have parkinsonism with scores of 15 or higher. At baseline, 199 were considered normal, with a score of 3 or lower; 306 had mild parkinsonian symptoms, with a mean UPDRS3 score of 10; and 76 qualified as having diagnosable parkinsonism with a mean UPDRS3 of 19.

Ms. Lundin compared UPDRS3 scores with total hours of welding exposure at baseline. She found a linear association, with risk increasing along

VITALS

Major Finding: Welders with long-term manganese exposure may be at an increased risk of developing parkinsonism.

Data Source: A prospective cohort study of 581 welders, and an imaging study of 20 welders, 20 Parkinson's disease patients, and 20 normal controls.

Disclosures: Ms. Lundin reported no financial disclosures. Dr. Criswell reported receiving research support from numerous pharmacologic companies; her study was funded by the Michael J. Fox Foundation for Parkinson's Research, the National Institutes of Health, the American Parkinson Disease Association, the Advanced Research Center at Washington University, the Greater St. Louis Chapter of the APDA, the McDonnell Center for Higher Brain Function, and the Barnes-Jewish Hospital Foundation. Dr. Martin has received speakers' honoraria from Allergan.

with total exposure.

Subjects considered normal had a mean age of 41 years and a total exposure of 18,300 hours. Those with mild parkinsonian symptoms were a mean of 46 years old and had a mean total exposure of 25,100 hours. Those with parkinsonism had a mean age of 48 years, with a mean total exposure of 26,800 hours.

The prevalence ratio also rose with increasing exposure. Those with a total of less than 2,900 hours were considered the reference group, with no increase over expected background rates. The prevalence of parkinsonism increased by 20% for those with a total exposure of 2,900-9,600 hours, by 40% with 9,600-26,400 hours of exposure, and by 60% with more than 26,400 hours.

None of these baseline differences in UPDRS3 scores and prevalence of parkinsonism were statistically significant, but they provided a trend strong enough to justify the 3-year follow-up, Ms. Lundin said in an interview. "We will follow this group to determine incident cases of Parkinson's symptoms and symptom progression. We also have some industrial hygienists working with us to collect samples of manganese [on surfaces] in the shipyard and in the air."

Further work will include comparison to a nonwelding reference group, as well as blood samples indicating exposure to manganese, cadmium, lead,

Continued on following page

Biomarkers Ratio Improves Parkinson's Diagnosis

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES

BARCELONA – The ratio of total tau over total alpha-synuclein gave a sensitivity of 89% and a specificity of 61% for discriminating Parkinson's disease from other neurodegenerative diseases in a prospective study of 181 patients.

This is the first time a combination biomarker has been used to identify Parkinson's disease patients among a group with related disorders, including Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia, Dr. Omar El-Agnaf said in an interview at the conference. The findings' implications could be important in both the clinic and the lab.

"It isn't perfect, and it's not yet clinically usable, but it's better than anything else we have at this point," Dr. El-Agnaf said. The ability to discriminate Parkinson's disease patients from those with other neurodegenerative disorders could allow earlier detection and earlier and possibly more effective treatment.

The study, which will soon appear in the journal *Movement Disorders*, was conducted by a group of researchers involved in the Parkinson's Progression Markers Initiative (PPMI), a 5-year project seeking to identify and validate biochemical and imaging markers for the disease.

Healthy neurons normally release the alpha-synuclein protein into interstitial fluid; it's thought to be important in presynaptic signaling. Decreasing levels may be related to neuronal damage, and in previous studies they have been associated with Parkinson's disease and dementia with Lewy bodies, said Dr. El-Agnaf, a biochemist and professor at the United Arab Emirates University, Al Ain. But these prior studies found conflicting evidence that alpha-synuclein alone ad-

VITALS

Major Finding: The ratio of total tau over alpha-synuclein discriminated Parkinson's patients from those with other neurodegenerative disorders, with a sensitivity of 89% and a specificity of 61%.

Data Source: A prospective cohort study of 181 patients, 32 of whom had Parkinson's disease.

Disclosures: The study was funded by the Michael J. Fox Foundation for Parkinson's Research. Dr. El-Agnaf had no financial disclosures.

equately identifies Parkinson's disease.

This is partially a result of the wide reference range for normal alpha-synuclein levels (5-40 ng/mL) and to its natural, age-related decline. Other factors might be different methods of sample collection, different antibodies used in the immunoassay, and even the age of the samples. In samples stored more than 120 months, the level of alpha-synuclein goes down significantly, he said.

Those earlier studies confirmed that Parkinson's patients tended to cluster in the lowest level of alpha-synuclein, but "there were huge overlaps" with other disorders, and even with normal controls, which Dr. El-Agnaf said negated any significant association with Parkinson's. "If this was going to become a clinically useful tool, we needed a better way to measure" the potential biomarker.

Dr. El-Agnaf and his colleagues have been pursuing alpha-synuclein as a Parkinson's biomarker since 2002. In 2010, the group found that Parkinson's patients expressed increased levels of the protein's oligomeric form. Oligomers usually form before more complex molecules, and their increased presence suggested that these species might be particularly useful in detecting Parkinson's in its earliest stages, he said.

The 2010 paper found that a ratio of alpha-synuclein oligomers to total alpha-synuclein had 89% sensitivity and 91%

specificity for Parkinson's patients, compared with those with progressive supranuclear palsy (*Neurology* 2010;75:1766-72). "The ratio measurement was a much better indicator, but there was still a large overlap" with Alzheimer's disease patients and normal controls.

His current study, still in press, sought to identify any clinically useful relationship between alpha-synuclein and the

biomarkers used in Alzheimer's research (amyloid beta 42, total tau, and phosphorylated tau). The study cohort comprised subjects with Parkinson's (38), Alzheimer's (48), dementia with Lewy bodies (32), frontotemporal dementia (31), and other neurologic disorders (32).

All of these patients donated cerebral spinal fluid, which underwent the same immunoassay.

All patients with a disorder had significantly lower alpha-synuclein than did control subjects, again showing its inability to adequately discriminate Parkinson's disease from other conditions. The story was no different with the other individual biomarkers tested; the group overlap was still too great for clinical usefulness.

"We then tried ratios again: amyloid beta 42, total tau, and phosphorylated tau over alpha-synuclein," Dr. El-Agnaf said. "Both forms of tau over alpha-synuclein distinguished the Parkinson's patients, who had significantly lower ratios than the other groups." Total tau over alpha-synuclein gave the best results, with a sensitivity of 89% and a specificity of 61%. ■

A First Step to Improving Diagnosis

One of the biggest challenges with Parkinson's disease is the ability to accurately diagnose it vs. other movement disorders.

This paper represents a first step toward solving the problem of differential diagnosis.

The next step will be to look at how these biomarkers might change in the patient over time. This is where the Parkinson's Progression Markers Initiative (PPMI) comes in, with its goal of identifying biomarkers of Parkinson's progression. The research of Dr. El-Agnaf and his colleagues, and other teams, is helping us build a cupboard of potential biomarkers that we have at our disposal. Research scientists can go to the PPMI and use the samples and data there to verify their hypotheses and initial findings in a different – and very

diverse – population from both the United States and Europe.

We recently announced the launch of the PPMI Data and Biospecimen Request process, which makes the data from recently diagnosed Parkinson's patients and healthy controls available to researchers.

If scientists use the PPMI data, they will be asked to provide annual updates on their analyses. These will then be publicly displayed on the PPMI Web site and integrated back into the database with the goal of rapidly identifying and validating the biomarkers we need.

MARK FRASIER, PH.D., is the director of research programs for the Michael J. Fox Foundation for Parkinson's Research, which organizes and funds the PPMI project.

VIEW ON THE NEWS

Continued from previous page

aluminum, copper and other metals. These analyses will be part of a multivariate regression that will control for age, she added.

The pallidal index, an imaging outcome, was one of the primary end points of a separate study of welding and Parkinson's disease (*Neurology* 2011;76:1296-301). The index is a ratio of T1-weighted imaging signal in the global pallidus, compared with a reference region of white matter.

Primary investigator Dr. Susan Criswell, also of Washington University, Seattle, conducted an imaging study of 20 asymptomatic welders, also primarily recruited from shipyards. These were compared with 20 subjects with idiopath-

ic Parkinson's disease and 20 normal controls. Positron emission tomography with 6-[¹⁸F]fluoro-L-dopa (FDOPA) measured dopaminergic presynaptic nerve terminal dysfunction in different brain regions in all of the participants.

The mean ages of the groups ranged from 45 to 55 years, but the difference was not statistically significant. The welders had a mean exposure of 30,968 hours. The average level of manganese in their blood was 20 mcg/L – twice the upper limit of normal.

At baseline, those with Parkinson's disease had a significantly higher mean UPDRS3 score (19.7) than did either welders (8) or normal controls

(1). The welders' mean UPDRS3 score was significantly higher than was the normal controls' score. But Dr. Criswell noted that welders were not significantly different from con-



The prevalence of parkinsonism rose with the total number of hours in which individuals had welded in their lifetime.

MS. LUNDIN

trols in terms of clinical parkinsonian symptoms.

Imaging revealed significantly higher pallidal index scores among welders than those of both control subjects and those with Parkinson's disease. This difference was significantly re-

lated to increased exposure hours, but not to blood manganese levels.

After the researchers controlled for age, dopaminergic function also differed significantly between the groups. Welders had nearly 12% lower dopaminergic uptake in the anterior putamen than did the other two groups. The uptake pattern also varied significantly from those with Parkinson's disease, measuring lowest in the caudate, followed by the anterior putamen and then the posterior putamen.

"This pattern was reversed from the idiopathic Parkinson's disease subject pattern," in which dopaminergic uptake was lowest in the posterior putamen, followed by the anterior putamen and finally, the caudate, Dr. Criswell said.

There were no significant interactions between dopaminergic uptake and pallidal index, manganese levels, and UPDRS3 scores.

However, Dr. Criswell noted, the decrease in dopaminergic uptake among welders suggests presynaptic nigrostriatal dysfunction.

The findings suggest that manganese preferentially affects dopaminergic neurons in the caudate, rather than the putamen, Dr. W.R. Wayne Martin wrote in an accompanying editorial (*Neurology* 2011;76:1286-7). "In Parkinson's disease, decreased caudate [dopaminergic uptake] correlates with impaired executive function," wrote Dr. Martin of the movement disorders clinic at Glenrose Rehabilitation Hospital in Edmonton, Alta. ■